PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification : Not classified

A2

(11) International Publication Number: **WO 95/10173**

(43) International Publication Date: 20 April 1995 (20.04.95)

(21) International Application Number: PCT/SE94/00915

(22) International Filing Date: 3 October 1994 (03.10.94)

(30) Priority Data:
9303369-4 12 October 1993 (12.10.93) SE

(71)(72) Applicant and Inventor: GUSTAFSSON, Lars, Erik [SE/SE]; Badhusvägen 8, S-165 71 Hässelby (SE).

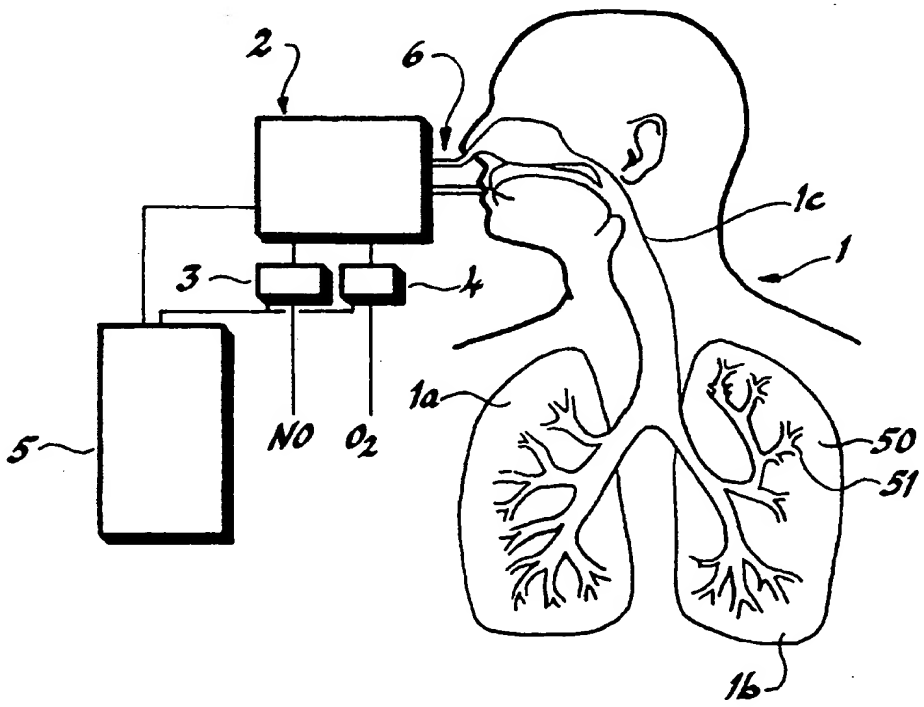
(74) Agent: LINDBLOM, Erik, J.; Flotthamn, S-150 23 Enhörna (SE).

(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ).

Published

In English translation (filed in Swedish).
With declaration under Article 17(2)(a).
Without classification and without abstract; title not checked by the International Searching Authority.

(54) Title: A RESPIRATORY ARRANGEMENT



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

A RESPIRATORY ARRANGEMENT.

TECHNICAL FIELD

The present invention relates to respiratory apparatus and then particularly, but not exclusively, to the type of apparatus by means of which a gaseous mixture can be delivered to and/or removed from the respiratory organs, such as the airways, of a living person, or a living creature such as a mammal, having one or more lungs.

In order to enable the respiratory apparatus to be applied within the concept of the present invention, it is necessary for the apparatus to include a number of nozzles or equivalent devices controlled by valves which, in turn, are controlled by a control unit, wherein the nozzles can be supplied with a relevant gas mixture with a predetermined ratio between the components of the gaseous mixture, this ratio being dependent on nozzle size, prevailing gas pressure, activation time, and other parameters.

One of the components of the gaseous mixture is typically nitric oxide.

DESCRIPTION OF THE BACKGROUND ART

The use of nitric oxide in the treatment of vasocontractions in mammals, and then particularly in human beings, and then particularly such contractions as those which derive from asthmatic conditions, is earlier known from International Patent Application No. PCT/US91/09111, having Publication No. WO 92/10228.

It is also known that the condition of asthmatics can be alleviated or cured when

a. the bronchus is enlarged;
b. when the blood circulation is improved; and

c. mastering other effects, such as by increasing cilia motility, increasing anti-inflammatory effects and/or inhibiting mediator release; this latter may be substance P, acetyl choline and/or histamine.

With regard to the singular features of the present invention, it can be mentioned that a number of different respiratory devices are known to the art, of which several will be used when carrying out the present invention. These devices have therefore not been described in detail, but have merely been considered as belonging to the prior art.

The present invention is based on an understanding that in the case of a healthy person, the concentration of nitric oxide, and particularly the time sequence or temporal sequence of the nitric oxide concentration, will vary during the expiration cycle, so as to lie initially at an elevated level and concentration, and then flatten out down to a plateau after only some few tenths of a second, and then decrease to zero upon completion of the expiration cycle.

It can be established that in respect of mammals, including human beings, who are prone to and at times suffer from asthmatic conditions, the nitric oxide content and the temporal variation in concentration is highly elevated initially in the expiration cycle, within some tenths of a second of its commencement, during those times in which the asthmatic conditions are not manifest or acute, and that the concentration flattens out to a plateau value which has been found to lie at or beneath the plateau value of a healthy being, and falls to zero at the end of the expiration cycle.

Furthermore, when inciting asthmatic conditions in test animals, while inducing the aforesaid variation in the concentration of nitric oxide, it has been established that contraction of the bronchus will increases when the body's own production of nitric oxide is blocked artificially.

It has also been established that the nitric oxide concentration of the expiration gas or air of smokers and other people whose lungs are chronically affected is lower than the concentration of nitric oxide in the air exhaled by people who are healthy in this respect.

Experiments carried out in practice have shown that this nitric oxide deficiency in the expiration air can be restored or improved by adding nitric oxide to the inspiration air.

SUMMARY OF THE PRESENT INVENTION

TECHNICAL PROBLEMS

It will be seen when studying the known prior art and the research carried out in this field that a technical problem resides in realizing the significance of providing a respiratory arrangement which is so adapted as to permit the concentration of nitric oxide in the gaseous mixture to vary during the inspiration cycle, therewith improving the condition of a suffering person and reducing the unpleasantness caused.

Another technical problem is one of providing a respiratory arrangement in which a gaseous mixture can be delivered to and/or removed from the airways and respiratory organs of a living person having one or more lungs such that the gaseous mixture can be given, through the medium of a number of nozzles and a control unit connected thereto, a predetermined ratio between the components of the gaseous mixture, the concentration in which these components are present and a temporal or time-wise variation in concentration, one of said components being nitric oxide (NO), and thereafter realizing that improved effects can be expected in asthmatic human beings when such an arrangement enables the nitric oxide contribution to the gaseous mixture to be varied in a manner that can be evaluated, at least during an inspiration cycle.

A technical problem also resides in the ability to realize that a higher amount of nitric oxide and a higher nitric oxide concentration should be introduced in the terminating phase of the inspiration cycle, so that the higher concentration will exist in the "dead space" and thus not in the alveolus cells, where poisoning might be likely to occur.

A technical problem is also one of realizing the significance of and the advantages afforded by allowing the nitric oxide proportion or concentration to be chosen as zero within the initial phase of the inspiration cycle.

It will be seen that a technical problem is one of realizing the possibilities that are associated with allowing the nitric oxide proportion or concentration to be chosen as high as 10,000 ppb to 100,000 ppb within the terminating phase of the inspiration cycle.

Another technical problem is one of realizing the possibilities associated with allowing the nitric oxide proportion to be chosen up to 40 ppb within the initial phase of the inspiration cycle, this nitric oxide proportion being intended to enter the alveolus cells.

Another technical problem is one of realizing how the nitric oxide proportion and its time-wise distribution shall be adapted to an asthmatic person.

It will also be seen that a technical problem relating to this treatment is one of realizing that the initial phase and the terminating phase of the inspiration cycle should be adapted mutually with equal or essentially equal volume contents, so as to adapt to the "dead space" and the total volume of the alveolus.

It will also be seen that a technical problem is one of realizing the advantages that are gained when the time

duration of the initial phase and the terminal phase of an inspiration cycle are mutually the same or essentially the same, and at least related to the person concerned.

It is not unusual for asthmatics to use a further component in addition to the nitric oxide concentration, which in such case may be oxygen.

SOLUTION

With the intention of solving one or more of the aforesaid technical problems, the present invention takes as its starting point a respiratory arrangement which is able to deliver a gaseous mixture to and/or remove a gaseous mixture from the airways and the respiratory organs of a living person having one or more lungs, by delivering the gaseous mixture through the medium of a number of nozzles at a predetermined ratio or concentration between the gas components, of which one is nitric oxide (NO).

In accordance with the invention, at least the contribution made by the nitric oxide concentration to the gaseous mixture can be varied during at least one inspiration cycle.

By way of proposed embodiments that lie within the scope of the present invention, it is proposed that the proportion of nitric oxide and its concentration is higher in the terminating phase of an inspiration cycle.

It is also proposed that the proportion of nitric oxide present is zero in the initial phase of an inspiration cycle.

With regard in particular to people who suffer from asthma, i.e. asthmatics, it is proposed that nitric oxide is present in an amount corresponding to 10,000-100,000 ppb in the terminating phase, whereas nitric oxide may be present in an amount corresponding to 40 ppb in the initial phase.

It is also proposed that the proportion of nitric oxide present and its time-wise distribution is adapted to an asthma-suffering person by adapting the time variation of the nitric oxide concentration in relation to the person's own production of nitric oxide.

It is also proposed that the initial phase and the terminating phase have the same or essentially the same volume content and/or that the initial phase and the terminating phase have the same or essentially the same time duration.

With the intention of easing the discomfort of asthmatics, it is normal to use a further component during treatment. This further component may be oxygen.

ADVANTAGES

Those advantages that are primarily associated with an arrangement of the kind intended reside in enabling the discomfort of asthmatics to be alleviated during an acute attack through the medium of a respiratory arrangement with which the proportion of nitric oxide delivered to the inspiration air and the time-wise distribution of the nitric oxide concentration as seen totally will coincide with the time distribution of the endogenous concentration of nitric oxide, problem free.

The arrangement also reduces the toxic effect of nitric oxide inspired in the alveoli, and reduces the effect of nitric oxide taken up by the alveoli, by which is meant the formation of methaemoglobin or the effect on the ability to supply blood.

The primary characteristic features of an inventive respiratory arrangement are set forth in the characterizing clause of

the following Claim 1.

BRIEF DESCRIPTION OF THE DRAWING

A preferred embodiment of a respiratory arrangement having the main characteristic features of the present invention will now be described in more detail with reference to the accompanying drawing, in which

Figure 1 illustrates schematically a respiratory arrangement connected to a person and including valves for supplying oxygen and/or nitric oxide;

Figure 2 is a time diagram concerning the time variation of the nitric oxide concentration in an expiration cycle of a healthy person;

Figure 3 is a similar diagram concerning a person suffering from asthma but who at the time of taking the measurements shown in the time diagram was not afflicted by bronchus- or vasoconstrictions or the like;

Figure 4 is a time diagram which shows the time variation of the nitric oxide concentration during an inspiration cycle; and

Figure 5 illustrates schematically an alveolus present in a lung, and a neighbouring bronchiole.

DESCRIPTION OF AN EXEMPLIFYING EMBODIMENT AT PRESENT PREFERRED

Figure 1 illustrates schematically a person 1 having two lungs 1a and 1b and being treated with the aid of a respiratory arrangement 2.

The respiratory arrangement 2 is constructed in a known manner for the delivery and/or the removal of a gas mixture to and from the airways 1c and general respiratory organs belonging to a person 1 having one or more lungs 1a and 1b, by adapting the concentrations of the gas components to a predetermined relationship in an inspiration cycle 6, through the medium of a number of nozzles 3 and 4 and valves controlled by a control unit 5.

Which of the components shall be included is decided from case to case, although it will be noted that in the case of the present invention, one of these components shall be nitric oxide (NO).

As Figure 4 is intended to show, the invention is based on a variation in at least the extent of the contribution made by the nitric oxide to the gas mixture during at least a complete inspiration cycle.

In this regard, it is shown that the proportion of nitric oxide is higher in the terminating phase 6b of an inspiration cycle.

It lies within the scope of the invention to vary the concentration of nitric oxide and the time-wise distribution and duration within wide limits.

For instance, the nitric oxide concentration may be zero in the initial phase 6a of the inspiration cycle.

According to the invention, the nitric oxide concentration in the latest part of the terminating phase may be from 10,000 to 100,000 ppb, whereas the nitric oxide concentration in the initial phase 6a may be up to 40 ppb.

Figure 2 is intended to show a variation in the nitric oxide concentration in time for a healthy person during an expira-

tion cycle. The diagram shows an initial peak value of about 20 ppb and a plateau at about 12 ppb.

Figure 3 is intended to illustrate the variation in the concentration of nitric oxide in relation to time in relation to a person who suffers from asthma but who at the time in question was not troubled by vasoconstrictions, phlegm or other conditions which would otherwise give discomfort. The diagram shows an extreme large concentration of nitric oxide initially, up to 80 ppb, and a lower concentration in the subsequent plateau, about 10 ppb.

According to the invention, it is possible through the medium of the control unit 5 to "tailor make" each proportion of nitric oxide and its time-wise or temporal distribution, and to adapt this directly to a person suffering from asthma.

It can be expected that the initial phase 6a and the terminating phase 6b can be adapted so as to have identical or essentially identical volumetric contents, or alternatively the initial phase and the terminating phase may be mutually adapted so as to have equal or essentially equal time durations.

Even though the exemplifying embodiment has been illustrated with reference to only one single further component, i.e. oxygen, it will be understood that the application of other gases or gaseous mixtures, such as oxygen and/or helium and/or air also lies within the scope of the present invention.

The reason for suggesting the division of an inspiration cycle into two phases 6a and 6b is because when inspiring, the first inspiration phase shall pass down to the alveoli, and possibly also down to the bronchiole 51, whereas the terminating phase 6b shall fill the "dead space" including upper and/or lower airways, which in the case of an adult can be calculated as 150 ml.

The invention is also based on the understanding that an ideal substitute therapy should resemble as far as possible the normal expiration pattern with regard to the time distribution of the nitric oxide concentration of healthy or relatively unaffected people but otherwise suffering no asthmatic symptoms.

The peak value shown in Figure 3 can rise as high as 550 ppb for some people.

It lies within the scope of the invention to first inhibit the body's own production of nitric oxide, by injecting or breathing in an NO-synthesis inhibitor, for instance methyl-arginines, nitroarginines, aminoguanidine or derivatives thereof, and then to cause the control unit 5 to generate an inspiration cycle with a well-balanced concentration distribution corresponding to the body's own production of nitric oxide and its temporal or time-wise distribution.

It should be noted that when a given distribution exists in the expiration cycle, the inspiration cycle shall time-wise be inverse, which Figures 3 and 4 are intended to illustrate.

Even though the description refers to only one single inspiration cycle and one single expiration cycle, it lies within the scope of the invention for the described time variation of the nitric oxide concentration to apply for one inspiration cycle among a predetermined number of cycles, of which the remainder are not given a nitric oxide addition.

The proportion of nitric oxide used and its temporal distribution may be adapted to a person suffering chronic breathing difficulties or acute lung damage or congenital damage to a lung function, or who suffers coincidence deficiency between lung blood flow and lung ventilation.

It will be understood that the invention is not restricted to

the aforedescribed and illustrated exemplifying embodiment of the invention since modifications can be made within the scope of the following Claims.

CLAIMS

1. A respiratory arrangement for delivering and/or removing a gas mixture to and from the airways and respiratory organs of a living being having one or more lungs, by giving the components of the gas mixture a predetermined ratio through the medium of a number of nozzles, of which components one is nitric oxide (NO), **characterized** in that the extent of the contribution made to the gas mixture by the nitric oxide can be varied at least during one inspiration cycle.

2. An arrangement according to Claim 1, **characterized** in that the proportion of nitric oxide is higher in the terminating phase of the inspiration cycle.

3. An arrangement according to Claim 1 or 2, **characterized** in that the proportion of nitric oxide in the initial phase of the inspiration cycle is zero.

4. An arrangement according to Claim 2, **characterized** in that the proportion of nitric oxide in the terminating phase of the inspiration cycle is between 10,000 to 100,000 ppb.

5. An arrangement according to Claim 3, **characterized** in that the proportion of nitric oxide in the initial phase is up to 40 ppb.

6. An arrangement according to any one of the preceding Claims, **characterized** in that the proportion of nitric oxide and its time-wise distribution is adapted for a being suffering from asthma.

7. An arrangement according to Claim 1, **characterized** in that the initial phase and the terminating phase have mutually the same or essentially the same volumetric contents.

8. An arrangement according to Claim 1, **characterized** in

that the initial phase and the terminating phase are mutually adapted so as to have the same or essentially the same time duration.

9. An arrangement according to Claim 1, **characterized** in that a further component is comprised of oxygen and/or helium and/or air.

10. An arrangement according to Claim 1 or 6, **characterized** in that the proportion of nitric oxide is adapted for a being suffering chronic breathing difficulties or acute lung damage or congenital damage to the lung function.

11. An arrangement according to Claim 6, **characterized** in that the proportion of nitric oxide is adapted for a being suffering a coincidental deficiency between lung blood flow and lung ventilation.

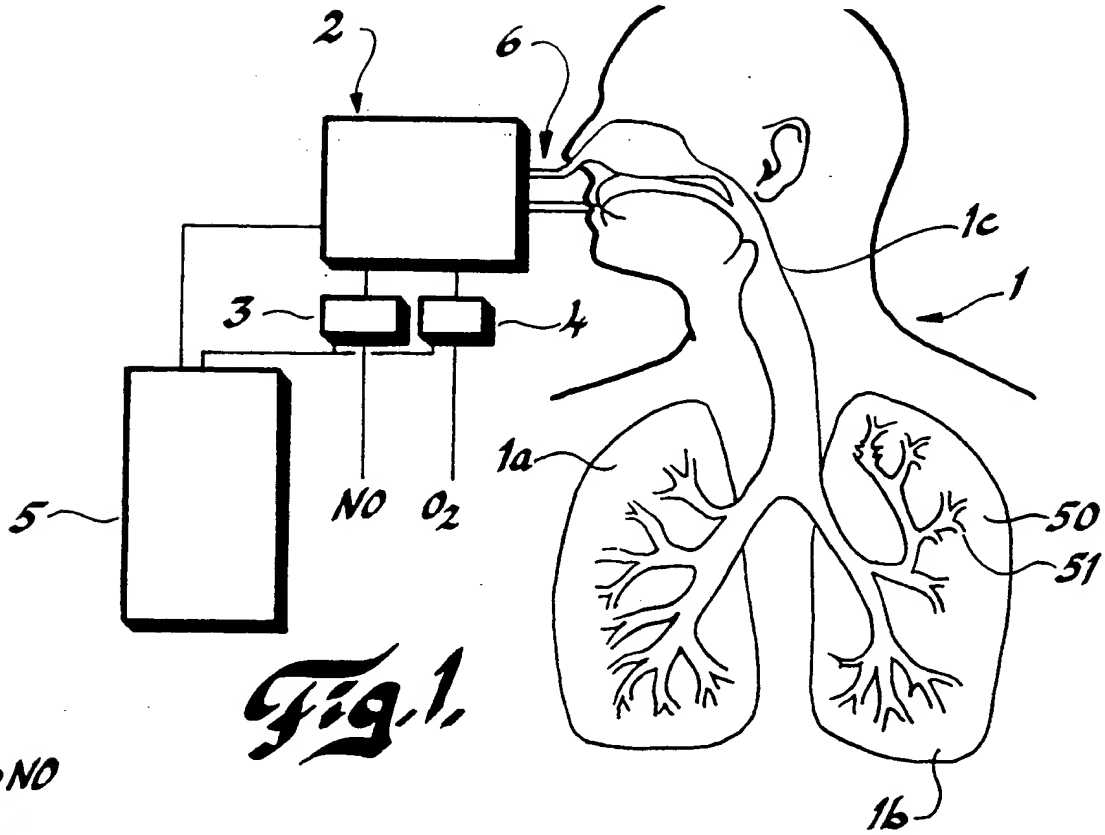


Fig.1.

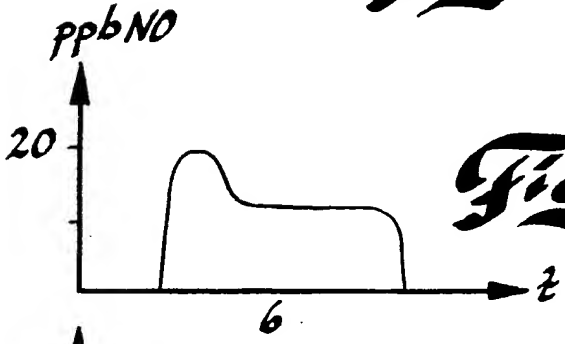


Fig.2.

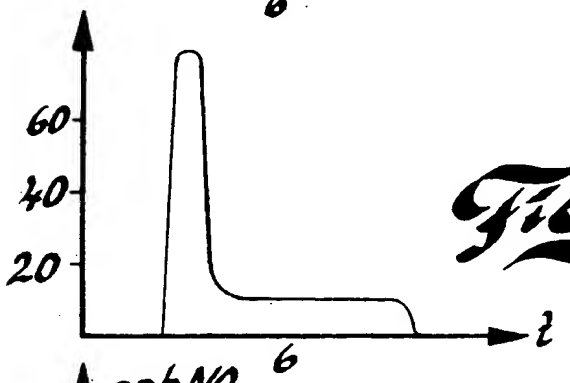


Fig.3.

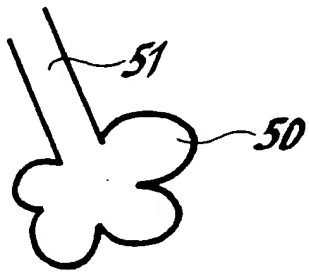


Fig.5.

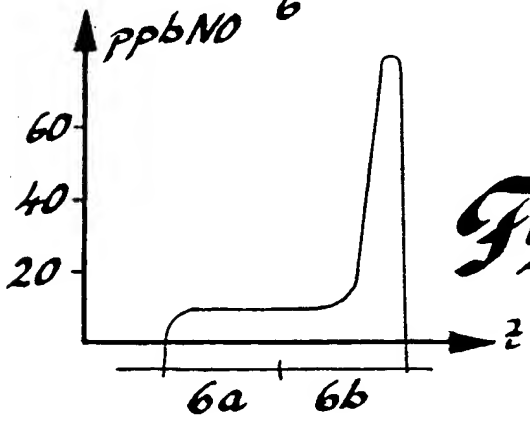


Fig.4.

PATENT COOPERATION TREATY

PCT

DECLARATION OF NON-ESTABLISHMENT OF INTERNATIONAL SEARCH REPORT

(PCT Article 17(2)(a) and Rule 39)

Applicant's or agent's file reference	IMPORTANT DECLARATION	Date of mailing *(day/month/year)*
93 03369-4 PCT		26 -01- 1995
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/SE 94/00915	3 October 1994	12 October 1993
International Patent Classification (IPC) or both national classification and IPC 6		
A61M 16/12		
Applicant		
GUSTAFSSON, Lars Erik		

This International Searching Authority hereby declares, according to Article 17(2)(a), that **no international search report will be established** on the international application for the reasons indicated below.

1. [X] The subject matter of the international application relates to:
   - a. [ ] scientific theories.
   - b. [ ] mathematical theories.
   - c. [ ] plant varieties.
   - d. [ ] animal varieties.
   - e. [ ] essentially biological processes for the production of plants and animals, other than microbiological processes and the products of such processes.
   - f. [ ] schemes, rules or methods of doing business.
   - g. [ ] schemes, rules or methods of performing purely mental acts.
   - h. [ ] schemes, rules or methods of playing games.
   - i. [X] methods for treatment of the human body by surgery or therapy.
   - j. [ ] methods for treatment of the animal body by surgery or therapy.
   - k. [ ] diagnostic methods practised on the human or animal body.
   - l. [ ] mere presentations of information.
   - m. [ ] computer programs for which this International Searching Authority is not equipped to search prior art.
2. [X] The failure of the following parts of the international application to comply with prescribed requirements prevents a meaningful search from being carried out:
   [ ] the description [X] the claims 1-11 [ ] the drawings
3. [ ] The failure of the nucleotide and/or amino acid sequence listing to comply with the prescribed requirements prevents a meaningful search from being carried out:
   - [ ] it does not comply with the prescribed standard
   - [ ] it is not in the prescribed machine readable form
4. Further comments:

   se annex sheet

Name and mailing address of the ISA/ SE	Authorized officer
Patent- och Registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. 08-667 72 88	Telex 17978 PATOREG-S	Anette Hall Telephone No. 08-782 25 00

Continuation from box 4. Further comments

International application No.
PCT/SE 94/00915

The claims relate to a respiratory arrangement characterized by features of the use to which the arrangement is to be put. Thus, the arrangement aquires the nature of a method of treatment carried out on the living human body. This is subject matter which the International Searching Authority is not required to search under Article 17(2)(a)(i) and Rule 39 (iv).